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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,739	04/30/2001	George Jackowski	2132.044	3449

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EXAMINER	
COOK, LISA V	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 09/24/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/845,739	JACKOWSKI ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 36-43* is/are pending in the application.

4a) Of the above claim(s) *1* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1 and 36-43* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicant's response to the Office Action mailed 07 April 2003 (Paper No. 17 filed 7/9/03) is acknowledged. In amendment-B filed therein claims 2-35 were cancelled without prejudice or disclaimer. Claim 1 was amended while new claims 36-43 were added. Currently claims 1 and 36-43 are pending.

2. Claim 1 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No.15 filed 2/4/03.

This application contains claim 1, which is drawn to an invention nonelected with traverse in Paper No.15 filed 2/4/03. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

3. All objections and rejections cited of record in paper #16 and not indicated here have been withdrawn in view of the amendments and arguments submitted July 9, 2003.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

4. Claims 36-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 36-40 are vague and indefinite because it is not clear as to what the biopolymer marker or analyte will entail. As cited the method is directed to a correlation of the unknown polymer with SEQ ID NO:1, however it is not clear as to what the final correlation will be. For example does the biopolymer correlate to SEQ ID NO:1 as a 100% match, 90% match, etc. Appropriate correction is required.

Double Patenting

5. Double patenting obviousness-type rejection:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 36-40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-9 of U.S. Patent No. 6,617,308 in view of Lewis et al. - Dale L. Oxender, Protein Structure, Folding, and Design 2, Alan R. Liss, Inc., New York, copyright 1987, pages 417-427. Although the conflicting claims are not identical, they are not patentably distinct from each other because both inventions are drawn to methods of comparing mass spectrum profiles of unknown peptides with the mass spectrum profile of a sequence identified as SEQ ID NO:1. Although the instant application is directed to a 15 amino acid structure differing in one terminal amino acid (Ser) the elimination of a terminal acid is taught not always critical for activity. On page 420 4th paragraph Lewis et al. teach that the N-terminal 6 amino acids were not required for activity in Il-3 molecules. Further Lewis et al. teach that smaller proteins and/or peptides can be purified more readily than the larger ones. See page 420 1st paragraph. Therefore, this invention is encompassed within Patent #6,617,308.

OBJECTIONS MAINTAINED

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 36-43 (previously 3-9, 18-28, and 33-35) remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 36-43 are broadly drawn to methods of determining the presence or absence of congestive heart failure by analyzing a biological sample obtained from a patient to identify a biopolymer marker sequence whose mass spectrum profile displays the characteristic profile of a sequence identified as SEQ ID NO:1. The specification also contemplates the use of these methods for diagnosing, staging, monitoring, prognosticating or determining predisposition to congestive heart failure.

These diagnostic methods include for example biopolymer evidencing, characterization, regulation, risk-assessment, and therapeutic identification. The specification asserts that the said target sequence was found in congestive heart failure. However, the obtained results set forth in the specification for example in figure 1 is not clearly indicative of congestive heart failure, because no control sample analysis is presented by way of example.

Further it is not clear how the same biopolymer marker will be utilized to distinguish any and all disease states. In other words how will one identify any disease state by detecting and comparing the mass spectral profiling of SEQ ID NO:1 with various peptides in a sample.

The specification does not enable one of ordinary skill in the art to definitively assess the incidence or further distinguish between any and all diseases including congestive heart failure in a single test sample. And while the evidence presented in the specification does point to the high occurrence of the sequence in congestive heart failure, this is not sufficient in implementing the said sequences in a molecular based diagnostic method for congestive heart failure and any other disease state with said sequence. Furthermore, Applicants have not provided any disclosure enabling the use of the biopolymer marker with regard to regulating the presence or absence of said sequence. There is no disclosure designating how the sequence bound in the method that could be regarded as enabling one of ordinary skill in the art to use the said sequences in the diagnostic method.

Applicants have not set forth any supporting evidence that suggests that any of the sequences (SEQ ID NO: 1) are unique molecular markers for congestive heart failure and all other possible disease states. Tascilar et al. (Annals of Oncology 10,Suppl. 4:S107-S110, 1999) reports on diagnostic methods in the realm of disease states, however this review article is relevant to Applicants' claimed invention. It is art known that molecular–based assays are valid tools used in predicting and detecting diseases, however as assessed in the Tascilar review "...these tests should be interpreted with caution...". and "the genetic changes found in sources other than the pancreas itself (blood, stool) should be evaluated prudently".

Furthermore, Tockman et al. (Cancer Research 52:2711s-2718s, 1992) teach considerations necessary for a suspected cancer biomarker (intermediate end point marker) to have efficacy and success in a clinical application.

Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders. Tockman teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials, see abstract. Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, column 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome.

The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. "This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point [marker]", see page 2714s, column 1, Biomarker Validation against Acknowledged Disease End Points section. Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials, see page 2716s, column 2, Summary section. Tockman reiterates that the predictability of the art in regards to cancer prognosis and the estimation of life expectancies within a population with a disease or disorder are highly speculative and unpredictable.

Based on the analysis and the teachings presented above it would require undue experimentation for the skilled artisan to practice this invention because there is no support in the specification for the enablement of the broadly claimed invention. Therefore, in view of the insufficient guidance in the specification, extensive experimentation would be required to enable the claims and to practice the invention as claimed.

Response to Arguments

8. Applicants argues that they are currently in the process of preparing a Declaration under 37 CFR 1.132 in order to provide evidence of the absence of the 1793 dalton biopolymer marker (SEQ ID NO:1) in normal human sera. Until receipt of the Declaration and review of the evidence the rejection is maintained.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claims 36-43 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial, credible or asserted utility or a well-established utility.

Claims 36-43 are broadly drawn to methods/kits of determining the presence or absence of a biopolymer marker having a mass spectral profile displaying the characteristic profile of SEQ ID NO:1 as an indicator of congestive heart failure. These diagnostic methods include for example biopolymer evidencing, characterization, regulation, risk-assessment, and therapeutic identification. The specification also contemplates the use of these methods for diagnosing, staging, monitoring, prognosticating or determining predisposition to congestive heart failure.

Applicants have disclosed in the specification that SEQ ID NO: 1 is measurable in patients with congestive heart failure. See figure 1. The specification also states that the said sequence was highly expressed in congestive heart failure, but undetectable in other tested disease related to Syndrome X, such as overt diabetes and kidney failure. See page 16, lines 9-18 and page 26 line 20 through page 27 lines 2. This is contradictory to information presented in the prior art regarding the utility of the same sequence, namely SEQ ID NO:1. U.S. Patent #5,849,297, U.S. Patent #6,221,657, and U.S. Patent #6,268,485 teache utility in myocardial ischemia, frostbite, burns, (column 7 lines 28-29); glomerulonehritis, haemolytic anemia, myasthenia gravis, and type II collagen induced arthritis (column 7 lines 34-35).

These results do not support Applicants' asserted use of the claimed methods/kits for detection of any disorder, particularly congestive heart failure. There are no disclosure or working examples that demonstrate the specifically asserted utility and evidences a substantial utility was well established at the time of filing. Further it is not clear how the same biopolymer marker will be utilized to distinguish various unrelated disease states. If the marker is measurable in various disease states how will it distinguish the disease states. It is not clear how one will assess the particular disease state. In other word will the patient have myocardial ischemia, frostbite, burns, glomerulonehritis, haemolytic anemia, myasthenia gravis, type II collagen induced arthritis, or congestive heart failure. The specification does not enable one of ordinary skill in the art to definitively assess the incidence or further distinguish between both diseases in a single test sample.

And while the evidence presented in the specification does point to the high occurrence of the sequence in congestive heart failure, this is not sufficient in implementing the said sequences in a molecular based diagnostic method for at least one disease state with the said sequence. Furthermore, Applicants have not provided any disclosure enabling the use of the biopolymer marker with regard to regulating the presence or absence of said sequence. There is no disclosure designating how the sequence bound in the method that could be regarded as enabling one of ordinary skill in the art to use the said sequences in the diagnostic method.

Applicants have not set forth any supporting evidence that suggests that any of the sequences (SEQ ID NO: 1) are unique molecular markers for congestive heart failure. Based on the analysis set forth above the specification does not exemplify sufficient findings that constitute a specific, substantial or credible utility.

Claims 36-43 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by a specific, substantial or credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Response to Argument

10. Applicant contends that SEQ ID NO:1 is detectable only in congestive heart failure but undetectable in other diseases related to syndrome X. Therefore utility is meet. This argument was carefully considered but not found persuasive because SEQ ID NO:1 is encompassed by US patent #6,617,308 wherein in the sequence is used as a marker for not only congestive heart failure but myocardial infarction and Type II diabetes. Thus it is not clear as to how the same marker is indicative of all the previously mentioned disorders. Accordingly, the rejection is maintained.

11. For reasons aforementioned, no claims are allowed.

12. New ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE NON-FINAL.**

corrected
LVCook
9/10/03

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 308-4556, which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (703) 305-0808. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lisa V. Cook
CM1-7B17
(703) 305-0808
9/10/03

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09/22/03